Applicant respectfully disagrees with the premise of the rejections, and specifically traverses the rejections for at least the following reasons:

> (A) The rejection equates the treatment of CHF symptoms with mortality reduction, but there is a recognized distinction between (i) treating quality of life or symptoms of CHF and (ii) treating CHF mortality; the references and the art as a whole recognized carvedilol for, at most, potential symptomatic treatment;
>
> (B) Surprisingly and unexpectedly, carvedilol substantially decreases CHF mortality, by about 67% according to certain clinical studies, while other beta-blockers actually worsen mortality and the standard therapy, ACE inhibitors, achieve only about 20% mortality reduction; and
>
> (C) Additional claimed features not addressed by the rejection are also not taught or suggested by the reference combinations.

A. TREATMENT FOR CHF SYMPTOMS IS DISTINCT FROM TREATMENT TO DECREASE A RISK OF CHF MORTALITY

The rejections rely on Metra for disclosing that carvedilol "decreases a risk of mortality in [CHF] patients." (Office Action, pg. 3 regarding section 102 rejection; *see also* pg. 4 regarding section 103 rejection[1].) Metra is cited in particular for disclosing "the administration of carvedilol to both reduce heart rate and also mean pulmonary artery and pulmonary wedge pressure in the short term, and, improve exercise left ventricular systolic function and reduce heart failure symptoms in the long term." (Office Action, pg. 3 (emphasis added).)

As expressly indicated by Metra, however, what is disclosed is the treatment of CHF symptoms. (Metra, pg. 1679, 1686.) Treatment of CHF mortality is distinct, and,

Applicant submits, would have been recognized as distinct at the time of Applicant's invention. At least in view of this distinction, discussed further below, reconsideration and withdrawal of the rejections based on Metra under section 102 and on the combination of Metra and Olsen under section 103 are respectfully requested.

1. Metra is directed to the treatment of CHF symptoms, not mortality reduction

Metra does not refer to using carvedilol for decreasing a risk of CHF mortality. Indeed, the evidence of record shows that "[Metra] would not teach a practicing cardiologist anything about the use of carvedilol for the treatment of CHF or reduction of mortality in patients suffering from CHF." (Affidavit of Dr. Mary Ann Lukas (March 7, 2002) at ¶89, Exhibit K of Applicant's December 28, 2004, IDS reference no. 128 ("Applicants' Record, Volume 3 of 7"), attached hereto as Exhibit 1.)

Instead, Metra is directed to the treatment of CHF symptoms and quality of life factors:

> In this study we evaluated... the effects of short- and long-term carvedilol administration on clinical symptoms, submaximal and maximal exercise capacity and rest and exercise hemodynamic variables in a group of patients with congestive heart failure caused by idiopathic dilated cardiomyopathy treated with digitalis, diuretic agents and angiotensin-converting enzyme inhibitors.

(Metra, pg. 1679, col. 1, above "Methods" (emphasis added).) Rather than teaching or suggesting carvedilol for decreasing a risk of CHF mortality, Metra concludes that carvedilol may improve certain CHF symptoms:

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[1] Metra's deficiencies discussed herein apply equally to the combination of Metra and Olsen, for at least the reason that Olsen has not been cited for and does not overcome Metra's failure to teach or suggest use of carvedilol to decrease CHF mortality.

> Peak exercise capacity is not significantly affected by either short- or long-term carvedilol administration, whereas a significant improvement in clinical symptoms, quality of life and submaximal exercise duration was detected after longer-term therapy.

(Metra, pg. 1686, col. 1 (emphasis added).) Furthermore, Metra states that short-term therapy with carvedilol causes a reduction in heart rate as well as arterial and ventricular pressures, and that long-term therapy with carvedilol causes further reduction in heart rate as well as arterial and ventricular pressure. (Metra, pg. 1685-6, col. 1.) As discussed further below, reduction in heart rate (cardiodepression) was understood to be contraindicated for CHF patients.

Although not identical in all respects, the present case has analogies with *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), copy enclosed as Exhibit 2, on appeal from an interference proceeding before the Board of Patent Appeals and Interferences. The count at issue in *Rapoport* read:

> A method for treatment of sleep apneas comprising administration of a therapeutically effective amount of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment . . . .

254 F.3d at 1056 (emphasis added). On appeal, the Federal Circuit interpreted the preamble phrase "for treatment of sleep apneas" to refer to sleep apnea treatment *per se*, not merely treatment of symptoms associated with sleep apnea. *Id.* at 1059. Specifically, one party in *Rapoport* had argued that the count was anticipated by a reference disclosing the use of the claimed compound for treatment of anxiety and breathing difficulty, which are symptoms of sleep apnea, even though the reference did not provide for treatment of sleep apnea itself. *Id. at 1061*. The Court rejected that

argument. While the reference mentioned the possibility of administering the compound to patients suffering from sleep apnea, "[t]here is no disclosure in the [prior art reference that the compound] is administered to patients suffering from sleep apnea with the intent to cure the underlying condition." *Id.* (emphasis added). Thus, since the claim was interpreted to require that the method be practiced with the intent to achieve the objective stated in the preamble, it was not anticipated by a reference lacking a teaching of treating sleep apnea.[2]

In the present case, therefore, even if the combination of Metra or the combination of Olsen and Metra is considered to teach or suggest the use of carvedilol to treat symptoms associated with or in the presence of CHF, since the references (individually or in combination) do not teach or suggest an intended method of treating to decrease a risk mortality resulting from congestive heart failure, as more specifically set forth in the pending claims, the references do not anticipate or render obvious the claimed subject matter.

Although the absence of any teaching or suggestion for using carvedilol for decreasing CHF mortality is reason enough for the rejections to be withdrawn, Applicant notes that the following additional evidence corroborates the recognized distinction between treating CHF symptoms, on the one hand, and decreasing CHF mortality, on the other hand.

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[2] In *Jansen v. Rexall Sundown, Inc.*, the Federal Circuit reaffirmed the holding of *Rapoport* that a claimed method of treatment is not invalidated by a prior art reference unless that reference provides for practicing the method with the intent to achieve the claimed objective. 342 F.3d 1329, 1333-34 (Fed. Cir. 2003) ("In other words, administering the claimed vitamins in the claimed doses for some purpose other than [the claimed] treating or preventing macrocytic-megaloblastic anemia is not practicing

2. There was no recognized relationship between symptomatic CHF treatment and reduced CHF mortality

As explained by Dr. Lukas, the prevailing dogma throughout the 1980's and until about 1997 was that beta-blockers were contraindicated for the treatment of CHF patients. (Exhibit 1 at ¶28, 44-45.) This view was supported by early clinical results where patients with angina and CHF worsened or did not improve with beta-blockers. (*Id.* at ¶¶28, 44-45, 55 (beta-blocker xamoterol was shown to worsen survival in patients with severe heart failure), 56 (beta-blocker metropolol was shown to improve exercise tolerance and cardiac function, but had no beneficial effect on mortality), 57 (no statistically significant decrease in mortality with beta-blocker bisoprolol).)

With regard to symptomatic treatment in particular, Dr. Lukas explains that "[c]linincal research has demonstrated that symptomatic improvement does not predict the effect of the treatment on mortality." (Exhibit 1 at ¶52, *see also* ¶¶46-51, 53-58.) For example, while the beta blocker xamoterol had been approved for use for symptomatic improvement of heart failure, it was shown to worsen survival in patients with severe heart failure. (*Id.* ¶ 55.) According to a study published in 1993, the beta blocker metoprolol demonstrated improvement in exercise tolerance and cardiac function, but had no effect on mortality. The state of the art[3] is further addressed by the

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the claimed method....") *See also Glaxo Group Ltd. v. Teva Pharma, Inc.,* 2004 U.S. Dist. LEXIS 16750, at *56-57 (D. Del. 2004).

[3] The state of art, including the understanding and perspective of one skilled in the art, is relevant both to considerations of how the disclosure of Metra would be understood by one skilled in the art in the context of the § 102 rejection as well as the § 103 rejection. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) ("[For there to be anticipation, t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. It is sometimes appropriate to consider extrinsic evidence to explain the disclosure of a reference. Such factual elaboration is necessarily of limited scope and probative value, for a finding of anticipation requires

October 1994, CIBIS publication, which states that "a progressively increasing dose of β-blocker in severe heart failure confers functional benefit. . . . However, improvement in survival while on β-blockade remains to be demonstrated." (CIBIS Investigators and Committees, "A Randomized Trial of Beta-Blockade in Heart Failure — The Cardiac Insufficiency Bisoprolol Study (CIBIS)," 90(4) Circulation, Vol. 1765-1773, at 1765 (1994) (emphasis added), reference no. 33 in Applicant's December 28, 2004, IDS.)

At least due to the recognized distinction between symptomatic treatment and treatment to decrease mortality risk, Applicant respectfully submits that one skilled in the art would not have understood any disclosure in Metra regarding carvedilol or symptomatic treatment using the same to be a teaching of or a suggestion for using carvedilol for decreasing a risk of mortality. Indeed, as Dr. Lukas attested, "[Metra] would not teach a practicing cardiologist anything about the use of carvedilol for the treatment of CHF or reduction of mortality in patients suffering from CHF." (Exhibit 1, ¶89.)

3. The art taught away from the use of beta blockers to treat CHF mortality

Citing to Metra for effects of reduced heart rate, short-term pressure reduction, improved exercise and tolerance, function, and long-term symptom reduction, a premise of the rejection is that Metra discloses use of carvedilol for the "reduction in risk of mortality in patients suffering from congestive heart failure." (Office Action, pg. 4.) Applicant notes, however, that prior to the discoveries forming the basis of the present

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that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in gaps in the reference.").

invention, the only recognized use of carvedilol in CHF patients was for the treatment of the symptoms of CHF, particularly hypertension (high blood pressure). (*See, e.g.,* Affidavit of Dr. Lukas at ¶21-29 (Exhibit 1).) For example, according to Metra "[p]eak exercise capacity is not significantly affected by... carvedilol administration," instead only "a significant improvement in clinical symptoms, quality of life, and sub-maximal exercise duration was detected after long-term therapy." (Metra, pg. 1686 (emphasis added).) The treatment of symptoms, such as high blood pressure, is intended to enhance patient quality of life factors, such as exercise capacity. (Lukas Affidavit, ¶¶ 34-39.) Symptomatic treatment, however, was not corrected with mortality treatment for CHF patients, and symptomatic treatment does not teach or suggest treatment for mortality. (*Id.* at ¶52.)

Indeed, contrary to the premise of the rejection, as further explained by Dr. Martin Wehling and discussed further below, clinical testing of beta blockers had failed to show any significant decrease in mortality in CHF patients prior to the present invention. (June 19, 1997, Declaration of Martin Wehling, M.D., ¶6 (attached hereto as Exhibit 3), originally submitted in the prosecution leading to Applicant's U.S. Patent No. 6,760,069 ("the '069 patent")[4].) Indeed, beta blockers were contraindicated in patients suffering from CHF because they were known to have undesirable cardiodepressive effects. (Wehling Declaration, ¶¶7-9; Lukas Affidavit, ¶¶ 44-45.) Thus, the use of carvedilol (a beta blocker) to treat mortality would have been counter to the expectations and experience of one skilled in the art, and would not have been obvious. Further, as evidenced by Dr. Wehling's Declaration, it would have been unexpected for

[4] A reissue of the '069 patent is currently co-pending as Application No. 10/721,020.

carvedilol to reduce mortality in CHF patients; the mortality reduction in initial testing of about 67% being particularly unexpected and fulfilling a long-felt need. (*E.g.,* Wehling Declaration ¶¶7, 10, 14, 18; Lukas Affidavit, ¶¶64, 65, 70.)

Based on the evidence, including the teaching away from using beta-blockers for CHF patients for mortality reduction, Applicant respectfully submits that the Metra and Olsen combination fails to render obvious the presently claimed invention. Further, even if the reference combination did establish a *prima facie* case of obviousness, the evidence of unexpected results and long-felt need attested to by Drs. Wehling, Lukas, and Shusterman and discussed further below merits a finding of non-obviousness.

B. CARVEDILOL HAS AN UNEXPECTEDLY HIGH RATE OF MORTALITY REDUCTION

When carvedilol is administered to CHF patients with an intent to treat CHF mortality, the compound provides unexpectedly high rates of mortality reduction. As noted previously, the fact that there is any mortality reduction at all would have been surprising given the prior experience that other beta-blockers increased mortality. Indeed, there would have been no reasonable expectation of success for CHF mortality risk reduction. Further, compared to ACE inhibitors, the standard CHF therapy that yields a mortality reduction of only about 20%, the mortality reduction by carvedilol is also surprising and unexpectedly high. (September 25, 1996, Declaration of Neil H. Shusterman, M.D., ¶ 7-8, attached as Exhibit 4.)

Specifically, as discussed above, in the first clinical study (the "GSK carvedilol study") to examine carvedilol's effects on mortality, a dramatic mortality reduction of about 67% was found for all cases in class II-IV CHF patients. A later larger-scale study

(the "COPERNICUS Study") focusing on CHF patients with severe heart failure confirmed the surprising ability of carvedilol to reduce mortality in CHF patients, finding a 35% mortality reduction in these severe-heart failure patients.

The fact that mortality reduction by carvedilol was unexpected is well documented in the history and literature both prior and subsequent to the February 8, 1995 foreign priority date for the present reissue application. The "GSK Carvedilol Study" referenced above was designed and commissioned to study effects of carvedilol in CHF patients on exercise tolerance as measured with various walking tests. (Affidavit of Dr. Mary Ann Lukas (March 7, 2002), ¶ 61 (Exhibit 1).) Given concerns about the use of beta-blockers in CHF patients, an independent Data Safety Monitoring Board ("DSMB") was utilized to monitor the effect of carvedilol on mortality to determine if patient safety was being compromised. (*Id.* at ¶ 62.) However, rather than showing the mortality increase that had been worried about, the GSK Carvedilol Study instead showed a dramatic decrease in the risk of mortality by about 65%. (*Id.* at ¶ 64.)

Based on this dramatic and unexpected decrease in the risk of mortality, the DSMB prematurely terminated the study because it would have been unethical to withhold carvedilol from the placebo-controlled patients. (*Id.* at ¶ 65.) The DSMB specifically recommended that all patients on the placebo arm of the study be offered carvedilol. (*Id.*)

The unexpected success of the GSK Carvedilol Study is documented in various contemporaneous reports. For example, the February 20, 1995 edition of *Chemistry and Industry* (London), No. 4, page 123 contained an article titled "SmithKline Beecham: unexpected success halts drug trial." (Reference no. 41 of Applicant's December 28,

2004, IDS.) As reported in this article, "An independent monitoring group has told [GSK] to halt US trials of [carvedilol] because it's more effective than expected." (*Id.*) The article quotes the DSMB as having stated "to continue administering placebo would be unethical in view of . . . preliminary reviews of the mortality data." (*Id.*)

The published results of the GSK Carvedilol Study further evidence the significant and unexpected mortality reduction that caused the DSMB to prematurely halt the study. (M. Packer *et al.*, "The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group," New England J Med. 334(21): 1349-55 (May 23, 1996), reference no. 70 of Applicant's December 28, 2004, IDS.) As reported by Packer, "[r]andomization [of patients for the study] began on April 29, 1993, and the study was stopped early on the recommendation of the [DSMB] of February 3, 1995. This decision was based on the finding of a significant effect of carvedilol on survival — an effect that exceeded all conventional boundaries used to stop clinical trials." (*Id.* at pg. 1350 (citations omitted).) As reported by Packer, the mortality reduction for patients having mild to severe CHF was 65%. (*Id.* at pg. 1350.)

The surprising benefits of carvedilol for mortality reduction were confirmed in a subsequent, larger-scale study, the "COPERNICUS study," focusing on patients with severe CHF. (Affidavit of Dr. Mary Ann Lukas (March 7, 2002), ¶ 69 (Exhibit 1).) The results of this study were published in M. Packer *et al.* "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," 344(22) New England J. Med., 1651-1658 (May 31, 2001) (Reference no. 99 of Applicant's December 28, 2004, IDS).) As reported therein, the only prior large-scale study of using a beta-blocker (bucindolol) in patients with

severe heart failure suggested that beta-blockers may adversely affect patients at the highest risk. (*Id.* at pg. 1651.) However, the COPERNICUS study showed that for patients with severe heart failure there was a 35% decrease in the risk of death using carvedilol as compared with placebo. (*Id.*) According to these results, "if physicians treated 1000 patients with severe heart failure similar to that in [the COPERNICUS study] with carvedilol for one year, approximately 70 premature deaths would be prevented." (*Id.* at 1657.)

For at least these reasons, Applicant respectfully submits that there would have been no reasonable expectation of success, as asserted in the Office Action. (Office Action, pg. 5.) Additionally, although Applicant maintains that Olsen in view of Metra fails to establish a *prima facie* case of obviousness, even if they (or any other reference combination) did so, the evidence of the unexpected results, including the quantitatively large decrease in mortality risk, compels a finding of non-obviousness.

C. ADDITIONAL FEATURES NOT TAUGHT OR SUGGESTED

Applicant notes that the Office's rejection under section 103 does not address claims other than 1, 7, 10, 20, and 26 (Office Action, pg. 4), and Applicant therefore respectfully maintains that a prima facie case of obviousness has also not been established against the remaining claims.

II. Conclusion

In view of the foregoing remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to contact Applicant's undersigned representative by telephone at (202) 408-4092 to discuss this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 2, 2007

By: _____
Mark J. Feldstein
Reg. No. 46,693

Exhibits

1 Affidavit of Dr. Mary Ann Lukas (March 7, 2002) (associated exhibits can be found at Exhibit K of Applicant's December 28, 2004, IDS reference no. 128 ("Applicants' Record, Volume 3 of 7")).

2 *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001).

3 Declaration of Martin Wehling, M.D. (June 19, 1997), from Application No. 08/483,635.

4 Declaration of Neil H. Shusterman, M.D (September 25, 1996), from Application No. 08/483,635.